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Risk of malignancy and biologic therapy in rheumatic inflammatory diseases: A single-center experience

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Abstract

Objectives: Biologic disease modifying anti-rheumatic drugs (bDMARDs) have significantly improved the care of patients with rheumatic muscle-skeletal disorders (RMDs). Considering their immunosuppressive action, a theoretical increase of malignancy risk has been a major concern in the last few decades. The objective of this study is to analyze the incidence of malignancies in a cohort of patients affected by rheumatoid arthritis (RA), psoriathic arthritis (PsA), and ankylosing spondylitis (AS) treated with bDMARDs.
Methods: The charts of bDMARD-treated RMD patients were reviewed, and data about bDMARD exposure and malignant cancers (excluding non-melanoma skin cancer) were collected.
Results: 921 patients were included (median age: 50.59 years, 66.67% females); 1374 bDMARD treatments were administered, 87.12% were tumor necrosis factor inhibitors. A total of 21 malignant neoplasms were detected in 21 patients (61.90% females, median age at cancer diagnosis: 64.99 years), 66.67% in RA patients, 19.05% in PsA, and 14.28% in AS. Among them, 10 patients (47.62%) were treated with etanercept, 6 patients (28.57%) with adalimumab, and 1 case each with tocilizumab, certolizumab, golimumab, infliximab, and abatacept. The most common malignancies that we found were lung cancers, ductal mammary carcinomas, melanomas, and lymphomas. The incidence rate (IR) of malignancies in our cohort was 3.47 per 1000 person-years (p-y); the higher IRs were in RA patients (5.13 per 1000 p-y), in males (4.21 per 1000 p-y), and in patients aged >70 years (10.14 per 1000 p-y).
Conclusions: The results of our study showed IR of malignancies in RMD patients treated with bDMARDs that is in agreement with literature data.

Keywords

biologics • rheumatoid arthritis • ankylosing spondylitis • psoriatic arthritis • cancer • malignancy

Background

Biologic disease modifying anti-rheumatic drugs (bDMARDs) are highly efficient in significantly improving the care of patients with inflammatory rheumatic muscle-skeletal disorders (RMD), like rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). However, the risk of treatment-related adverse events is a reality worrying both patients and drug providers. In particular, the risk of malignancy has been a major concern in the last decade. Traditionally, bDMARDs down-regulate the immune response, which is an important host mechanism in the control of cancer progression and, therefore, might theoretically affect risk of cancer incidence. On the other hand, chronic exposure to systemic inflammation has also been considered as a risk factor for cancer development, as it might increase cell proliferation, mutagenesis, oncogene activation, and angiogenesis.[1]

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Currently, there is a great amount of data regarding tumor necrosis factor inhibitor (TNFi), showing that its use is not associated with increased risk of cancers, while controversial results for non-melanoma skin cancer (NMSC) and lymphoma are reported.[2–6] These results are confirmed in subgroup analyses by underlying condition (RA, PsA, or AS) and type of TNFi agent (adalimumab, certolizumab, etanercept, golimumab, or infliximab), also considering the higher versus lower dosages.[5] Other bDMARDs have also been investigated: data on rituximab were reassuring even in patients with recent malignancies, and tocilizumab as well did not show any increased risk of malignancies.[3,7,8] Other reports highlighted the increased risk of melanoma during abatacept treatment.[6]

The aim of our study was to analyze the incidence of malignancies in a cohort of patients affected by RA, PsA, and AS treated with bDMARDs.

Patients and Methods

A retrospective study on patients followed at the Rheumatology Outpatient Clinic Azienda Ospedaliero Universitaria Careggi, Florence (Italy) was performed between 01/01/2000 and 31/12/2015. In the study, we included patients with the diagnosis of RA, PsA, and AS treated with bDMARDs, either TNFi (etanercept, adalimumab, certolizumab, golimumab, infliximab) or non-TNFi (abatacept, tocilizumab, rituximab, anakinra, ustekinumab), according to international guidelines and on-label prescriptions. The study was approved by local institutional review board (IRB) (CAEVC protocol 15659), and patients signed informed consent.

A dedicated Microsoft Access database was created, including baseline demographics (date of birth, sex, diagnosis and date of diagnosis, comorbidities), bDMARD (date of beginning of bDMARD, name of bDMARD, date of interruption and reason), and malignancy (type of malignancy, histological result, date of diagnosis, and years of exposition to bDMARD at the time of cancer diagnosis) data.

Patients with benign neoplasms and patients with cutaneous carcinomas different from melanoma skin cancers (MSCs) were excluded, because these malignancies are not recorded in local regional registries, such as the Associazione Italiana Registro Tumori (AIRTUM).[8] It is known that NMSCs are indolent malignancies often diagnosed occasionally many years after the onset and treated on an outpatient basis from dermatologists. For this reason, these malignancies are poorly traceable and, consequently, are underestimated with fluctuations in incidence rates.

Statistical analysis was performed using Statistical Analysis System (SAS) software, version 9.3.

For each continuous variable, medians and interquartile ranges (IRs) are reported, while for categorical variables, absolute frequencies and percentages for each category are reported. Number of malignancies for 1000 person-year is calculated overall and stratified for gender, age, and diagnosis.

Results

A total of 921 patients were included in the analysis, with median age of 50.59 years (IR = 36.63–61.51 years) at the beginning of the first bDMARD and a prevalence of female gender (614 females, 66.67%).

During a median bDMARD exposure time of 5.17 years (IR = 2.20–8.47 years), the majority of patients in the study cohort were exposed to 1 bDMARD only (617 patients, 66.99%), 211 patients (22.91%) were treated with 2 biologics, and 63 patients (6.84%) with 3 biologics. The remaining 30 patients (3.26%) were exposed to ≥4 bDMARDs. In Table 1, the

Table 1: Characteristics of the study population

Characteristics	Total	RA	PsA	AS
No. of patients, *n* (%)	921 (100)	468 (50.82)	237 (25.73)	216 (23.45)
F, *n* (%)	614 (66.67)	379 (80.98)	143 (60.34)	92 (42.59)
M, *n* (%)	307 (33.33)	89 (19.02)	94 (39.66)	124 (57.41)
Median age, years (IR)	50.59 (36.63–61.51)	53.21 (37.68–64.24)	50.99 (41.09–60.53)	42.24 (32.45–52.82)
No. of bDMARDs during observation, *n* (%)				
1	617 (66.99)	293 (62.61)	171 (72.15)	153 (70.83)
2	211 (22.91)	115 (24.57)	49 (20.68)	47 (21.76)
3	63 (6.84)	40 (8.55)	11 (4.64)	12 (5.56)
4	17 (1.85)	11 (2.35)	4 (1.69)	2 (0.93)
5	11 (1.19)	8 (1.71)	1 (0.42)	2 (0.93)
6	2 (0.22)	1 (0.21)	1 (0.42)	0
Median time of exposure to bDMARDs, median years (IR)	5.17 (2.20–8.47)	5.66 (2.63–8.17)	4.11 (1.90–7.61)	5.13 (2.05–9.10)

F, female sex; M, male sex; IR, interquartile range; bDMARD, biologic disease modifying anti-rheumatic drug; RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis.

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characteristics of the study population, also divided according to the 3 diseases (RA, PsA, and AS), are reported.

A total of 1374 bDMARD treatments were administered. The majority was represented by TNFi (*n* = 1197, 87.12%): etanercept (*n* = 503, 36.61%), adalimumab (*n* = 388, 28.24%), infliximab (*n* = 167, 12.15%), golimumab (*n* = 99, 7.21%), and certolizumab (*n* = 40, 2.91%). The remaining 177 patients (12.88%) were divided into 89 abatacept (6.48%), 47 tocilizumab (3.42%), 36 rituximab (2.62%), 4 ustekinumab (0.30%), and 1 anakinra (0.07%) users.

A total of 21 malignant neoplasms, excluding NMSCs, were detected in 21 patients (2.28% of the study population), with a female prevalence (13 patients, 61.90%). The median age of these patients was 61 years (IR = 57–63 years), with a median age at cancer diagnosis of 64.99 years (IR = 60.42–68.99 years). The distribution of the malignancies among age clusters showed the majority of cases (17 cases, 80.95%) between 40 and 70 years of age, and the remaining 4 cases (19.05%) in patients >70 years old. In patients <40 years of age, no cases of malignancy were found.

Considering the underlying RMD, 14 patients (66.67%) were affected by RA, and the rest were similarly divided between PsA (4 patients) and AS (3 patients).

Almost half of the population that developed a malignancy was treated with etanercept at the moment of cancer diagnosis (10 patients, 47.62%), while 6 patients were receiving adalimumab (28.57%) and 1 case each received tocilizumab, certolizumab, golimumab, infliximab, and abatacept. The median time between the beginning of bDMARD treatment and the onset of malignancy was 2.42 years (IR = 1.50–4.25 years). The majority of patients (61.9%) at the moment of cancer diagnosis were undergoing treatment with the first bDMARD agent; only 38.1% of patients developed malignancy during the second. The median time between the beginning of bDMARD and the onset of malignancy was 2.42 years (IR = 1.50–4.25 years) in the whole cohort, with a value of 3 years (IR = 1.83–4.33 years) for the 10 patients treated with etanercept and 1.83 years (IR = 1.00–2.00 years) for the adalimumab-treated group. The characteristics of the cohort that develop a malignancy during the period of observation are reported in Table 2.

Analyzing the malignancies observed in our cohort (Table 3), we found the following: 5 lung cancers (23.81%), 3 ductal mammary carcinomas (14.29%), 2 malignant cutaneous melanomas (9.52%), 2 cases of lymphoma (1 intestinal lymphoma and 1 non-Hodgkin lymphoma of parotid gland), and 1 case (4.76% each) of liposarcoma, tongue cancer, hepatic cancer, colon adenocarcinoma, myeloid leukemia, endometrial adenocarcinoma, gastric cancer, papillary bladder cancer, and larynx cancer.

Table 2: Characteristics of patients that developed malignancy during the observational period

Characteristics	Total
No. of patients, *n*	21
Sex (F:M)	13:8
Median age at cancer diagnosis, years (IR)	64.99 (60.42–68.99).
Distribution of cases in age clusters, *n* (%)	
< 40 years	0
40–70 years	17 (80.95)
>70 years	4 (19.05)
Disease, *n* (%)	
RA	14 (66.67)
PsA	4 (19.05)
AS	3 (14.28)
No. of bDMARDs during observation, *n* (%)	
1	13 (61.9)
2	8 (38.1)
Total exposure to bDMARDs, median years (IR)	7.84 (3.79–12.83)
bDMARD at cancer diagnosis, *n* (%)	
Etanercept	10 (47.62)
Adalimumab	6 (28.57)
Golimumab	1 (4.76)
Infliximab	1 (4.76)
Certolizumab	1 (4.76)
Abatacept	1 (4.76)
Tocilizumab	1 (4.76)
Time from beginning of current bDMARD to malignancy (months; years)	2.42 (IR = 1.50–4.25)

F, female sex; M, male sex; IR, interquartile range; bDMARD, biologic disease modifying anti-rheumatic drug; RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis.

In our cohort, the incidence rate (IR) of malignancies was 3.47 per 1000 person-years (p-y). In Table 4, we report the IR of malignancies in the studied cohort, both global and stratified according to the rheumatologic condition, sex, and age. These data show that IR was higher in RA patients (5.13 per 1000 p-y), in males (4.21 per 1000 p-y), and in patients aged >70 years (10.14 per 1000 p-y).

Discussion

A correct evaluation of the neoplastic risk potentially associated with the use of bDMARDs is highly complex and challenging. This is due to many reasons, in particular, the high incidence of malignancies in the general population. In fact, according to the annual report of AIRTUM, it is estimated that 1 out of 3 women and 1 out of 2 men in Italy will develop

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Table 3: Number and types of cancers and bDMARDs assumed

Type of cancer	No. of patients, *n* (%)	bDMARDs at diagnosis
Lung cancer	5 (23.81)	3 ETA; 1 ADA; 1 GOL
Breast cancer	3 (14.29)	2 ETA; 1 CTZ
Melanoma	2 (9.52)	2 ADA
Lymphoma	2 (9.52)	1 ETA; 1 ADA
Liposarcoma	1 (4.76)	ETA
Tongue carcinoma	1 (4.76)	ETA
Hepatic cancer	1 (4.76)	TCZ
Colon adenocarcinoma	1 (4.76)	ETA
Myeloid leukemia	1 (4.76)	ADA
Endometrial adenocarcinoma	1 (4.76)	ADA
Gastric cancer	1 (4.76)	IFX
Papillary bladder cancer	1 (4.76)	ABA
Larynx cancer	1 (4.76)	ETA

ETA, etanercept; ADA, adalimumab; GOL, golimumab; CTZ, certolizumab; TCZ, tocilizumab; IFX, infliximab; ABA, abatacept; bDMARD, biologic disease modifying anti-rheumatic drug.

Table 4: Cancer incidence rates

Characteristics	No. of cases	No. of patients in general cohort	p-y	IR (1000 p-y)
Total, *n*	21	921	6049.14	3.47
Gender, *n*				
Female	13	614	4151.23	3.13
Male	8	307	1897.91	4.21
Age				
<40 years	0		1738.47	0
40–70 years	17		3913.53	4.34
>70 years	4		394.27	10.14
Diagnosis				
RA	14	468	2730.22	5.13
PsA	4	237	2055.06	1.95
AS	3	216	1263.86	2.37

p-y, person-years; IR, incidence rate; RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis.

a cancer during their lifetimes. For breast and prostate cancers, the most frequent in each gender, the probability is 1 out of 8; for lung cancer, 1 out of 10 in men and 1 out of 37 in women, while for colorectal cancer, 1 out of 11 in men and 1 out of 18 in women.

In addition, rheumatic diseases are associated with an intrinsic neoplastic risk, due to the chronic inflammatory status. An association between hematologic cancers and RA was first reported in a study published in 1982.[9] After this report, a considerable amount of evidence supporting the view of RA as a condition with an increased malignancy risk has emerged. Two meta-analyses by Smitten *et al.*[10] and Simon *et al.*[11] showed a small increased risk of overall malignancies in RA patients, compared with the general population, and found a pattern of risk for site specific malignancies, in particular, lymphoma and lung cancer, with a standardized incidence ratio (SIR) of 2.08 and 1.63, respectively; these data were confirmed in a more recent study on a Swedish cohort.[11] One of the mechanisms underlying the increased risk of lymphoma in RA patients include the presence of a persistent immunologic stimulation, possible leading to a clonal selection and malignant transformation of immune system cells and to a reduction of number and function of T-suppressor lymphocytes and of natural killer cell activity. Extra-skeletal manifestations of RA, in particular Felty's syndrome and Sjogren's syndrome, confer a further increase in the risk of developing non-Hodgkin lymphomas.[12] The observed association between RA and lung cancer may result from chronic lung inflammation and/or the presence of interstitial lung disease related to RA. In addition, cigarette smoking is a risk factor for RA and lung cancer and would explain an indirect association between them.[10,11] The risk of lymphoma and lung cancer has been hypothesized to be dependent on the level of disease activity.[11] A reduction of risk to develop colorectal and breast cancer in RA patients compared to general population has emerged. In particular, the reduced risk of colorectal cancer was attributed to the long-term use of non-steroidal anti-inflammatory drugs in RA patients.[10]

In spondyloarthropathies, the neoplastic risk has been less studied than in RA but an increase of overall malignancy risk in PsA and AS patients compared to general population still emerges from the literature.[12,13] More specifically, this emerges in breast cancer for PsA,[12] digestive system malignancies for AS,[13] and hematologic malignancies for both.[13,14]

Given the neoplastic risk in RMD per se, whether there is evidence of a direct effect of bDMARDs in the development of malignancies is still an open question. Immunosuppressive therapy would, in fact, be expected to favor uncontrolled cell growth. However, current evidences support inflammation as a key component for the tumor initiation and progression and, conversely, that the reduction of systemic inflammation would result in a decreased neoplastic risk in these conditions. In 2006, Bongartz *et al.*[15] published the first meta-analysis of randomized controlled trials suggesting a dose-dependent increase of malignancy risk in RA patients treated with TNFi (adalimumab and infliximab), mainly of lymphomas. Later, a similar meta-analysis on etanercept in RA showed a non-statistically significant increase of malignancy risk.[16] Finally, data from recent meta-analysis of RA registries have not found any increase in the overall cancer risk in the patients treated with TNFi compared to non-treated patients[2,5,17–22] or to the patients treated with conventional synthetic DMARDs (csDMARDs).[22] A significantly increased risk for all cancers was observed when comparing the TNFi-treated RA patients with the general population.[23] These results suggest that increased malignancy risk could be associated with disease

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activity rather than with treatment. Also, for PsA and AS patients treated with TNFi, literature evidenced a non-increased malignancy risk compared to the general population.[5,17,21,24]

Contrasting results about site-specific cancers are available, in particular regarding skin and hematologic neoplasms in RA patients. A large meta-analysis of 74 trials showed an increased risk of NMSC in RA patients with a HR of 2.02 (95% CI, 1.11–3.95),[24] not confirmed by another meta-analyses including fewer studies.[25,26] Data from the ARTIS registry confirmed the increased risk of NMSC in RA patients, in particular for basal cell cancer[27] and for melanomas, unlike previous meta-analyses.[17] In RA patients treated with TNFi, concerning the risk of lymphoma, the study of Berghen *et al*.[28] suggested an increased risk of lymphoma but the results from BSRBR-RA registry did not corroborate this result.[29]

Other bDMARDs have been much less studied, but the data from meta-analyses and long-term extension studies showed no increased overall malignancy risk for rituximab, abatacept, and tocilizumab.[21,25,30–33] Recently, other studies suggested that abatacept use is associated with a slight increase in skin cancer risk, both NMSC[34] and MSC.[6]

In our cohort, the IR of malignancy was 3.47 per 1000 p-y, with a higher value was found in the RA subgroup (5.2 per 1000 p-y). These results are in line with literature data: the meta-analysis of Chen *et al*.[2] showed an IR of 5.1–13.8 per 1000 p-y in RA patients treated with TNFi, while the study of an Italian group found an IR of 8.7 per 1000 p-y.[19] In addition, we found a high IR in patients aged >70 years, according to the fact that age is one of the most important neoplastic risk factors.

The most frequent malignancies in our cohort were lung and breast cancer, which are among the commonest also in the general population, followed by melanomas and lymphomas, which are suspected to be more frequent in TNFi-treated patients.

The strength of this study is the large cohort of patients enrolled, including a wide number of bDMARDs and malignancies. However, there are also many limitations: first of all, the observational retrospective nature of the study and the problem of missing data associated with it. Moreover, we did not collect data about concomitant drugs, such as corticosteroids and csDMARDs, which could also have an influence on the malignancy risk. In fact, a study on a cohort from Taiwan showed that RA patients had an increased risk of NMSC, in particular (i) those receiving higher doses of corticosteroids, methotrexate, and hydroxychloroquine and (ii) those receiving more types of DMARDs in combination or in sequence.[35] In addition, we have registered only a small number of malignancies in patients treated with non-TNFi (1 case related to abatacept and 1 case to tocilizumab).

In the future, it would be interesting to expand the patient cohort to add more information about comorbidities and concomitant medications in order to also examine other possible cancer risk factors and to compare our data with the risk of the general population.

Conclusions

Our data analyze the risk of cancer on a large cohort of patients affected by RMD and treated with bDMARDs, observed for a long follow-up. Despite the abovementioned limitations, the results of our study are in agreement with the literature data, in particular, regarding cancer IR. Further studies to analyze the roles of csDMARDs, comorbidities, and all the bDMARDs, both TNFi and non-TNFi, are warranted.

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Declarations

None.

Conflict of Interest

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Ethical Statement

None.

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